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Safety and Efficacy of Adenosine 5'-Triphosphate as a Hyperemic Agent for the Assessment of Peripheral Fractional Flow Reserve

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Abstract: The myocardial fractional flow reserve (FFR) is a useful measure of physiological stenosis in the coronary artery. Previous reports have identified peripheral FFR (pFFR) as another useful measure in peripheral artery disease (PAD); however, the vasodilators used to obtain maximal hyperemia varied among studies. The present study was conducted to identify the ideal vasodilator and vasodilator dose for pFFR assessment. We enrolled 24 patients with 26 lesions, comprising 14 lesions of the iliac artery and 12 lesions of the superficial femoral artery (SFA). After measuring the mean aortic pressure (Pa), the guidewire was advanced across the lesion and the mean distal pressure (Pd) was measured at the baseline Pd / Pa. A 100-μg dose of adenosine 5'-triphosphate (ATP) was then administered to obtain a pFFR with a washout interval of 5 to 10 minutes. Next, 200 μg of ATP, 10 mg of papaverine hydrochloride, or 1.5 mg of isosorbide dinitrate was administered before the final pFFR measurement. The baseline Pd / Pa (0.88 ± 0.08) was significantly decreased after each vasodilator ($P < 0.0001$), but there was no significant difference in pFFR among vasodilators ($P = 0.7569$). The study was discontinued in two patients with SFA lesions due to decreased systemic blood pressure after vasodilator administration. The hyperemic efficacy of 100 μg of ATP administered intra-arterially was similar to the efficacies of 200 μg of ATP, 10 mg of papaverine hydrochloride, and 1.5 mg of isosorbide dinitrate. Given the milder side effects of ATP versus other vasodilators, an intra-arterial dose of ATP 100 μg may be optimal as a first-line agent for pFFR measurement.

Key words: peripheral artery disease, endovascular treatment, fractional flow reserve, physiological stenosis, adenosine 5'-triphosphate

Introduction

Stent implantation has improved the initial and long-term outcomes of endovascular treatment (EVT) in both the iliac artery and superficial femoral artery (SFA) in patients with peripheral

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artery disease (PAD). The TASC II guidelines recommend EVT for TASC A- & B-type lesions, which show short- or middle-length stenosis and short chronic total occlusion[1]. While the ankle brachial index (ABI) and exercise ABI are established measures to evaluate ischemia in the whole limb of PAD patients, evaluating culprit lesions is sometimes very difficult in patients with multiple lesions or angiographically moderate stenotic lesions. EVT for non-significant stenotic lesions confers no symptomatic improvement and can induce harmful events.

The fractional flow reserve (FFR) is an established measure for estimating physiological stenosis in coronary artery disease[2]. The measurement and assessment of myocardium FFR is a useful procedure for reducing the rate of major adverse cardiovascular events in percutaneous coronary intervention (PCI)[3]. Vasodilator administration to maximize hyperemia of the myocardium is key to the correct measurement of FFR. In coronary artery disease, intracoronary papaverine and intravenous adenosine 5'-triphosphate (ATP) are usually administered as vasodilators to induce maximal hyperemia when assessing diffuse coronary atherosclerosis[4].

In contrast, the EVT guidelines[1,5] recommend pressure measurements across lesions both at rest and during hyperemia induction in cases with unclear hemodynamic significance of the target lesion. At the same time, several reports[6–15] have advocated peripheral FFR (pFFR) for evaluating the significance of stenosis versus that of peak systolic pressure or catheter-derived pressure gradients; however the vasodilators used varied among these studies, and there is no standard vasodilator defined for obtaining maximal hyperemia. The present study thus sought to identify the ideal vasodilator and dose for measuring pFFR without side effects.

Methods

Patient population

This investigation was a retrospective, single center study conducted at Showa University Fujigaoka Hospital including adult patients (> 20 years of age) with intermittent claudication or critical limb ischemia who underwent lower extremity artery echo or enhanced computed tomography. Patients suspected of having significant stenosis of the iliac artery or SFA underwent EVT. In cases of moderate stenosis, pFFR was performed to judge whether it is significant stenosis or not. Patients with acute limb ischemia, TASC II type C or D lesions, no patent arteries below the knee, or lesions with more than 90% stenosis on angiography were excluded from this study. TASC II C & D lesions were defined as those with long or multiple stenosis and long chronic total occlusion with or without calcification. The 24 patients (26 lesions) who met the inclusion criteria were enrolled in the study from January 2012 to December 2016.

The institutional review board of our hospital approved the study protocol, and all patients provided informed consent.

pFFR measurement

EVT was performed under local anesthesia using a 4 or 6 French (Fr) guiding sheath (Parent Plus®, Medikit, Tokyo, Japan) for treatment introduced via the ipsilateral approach or a 6 Fr

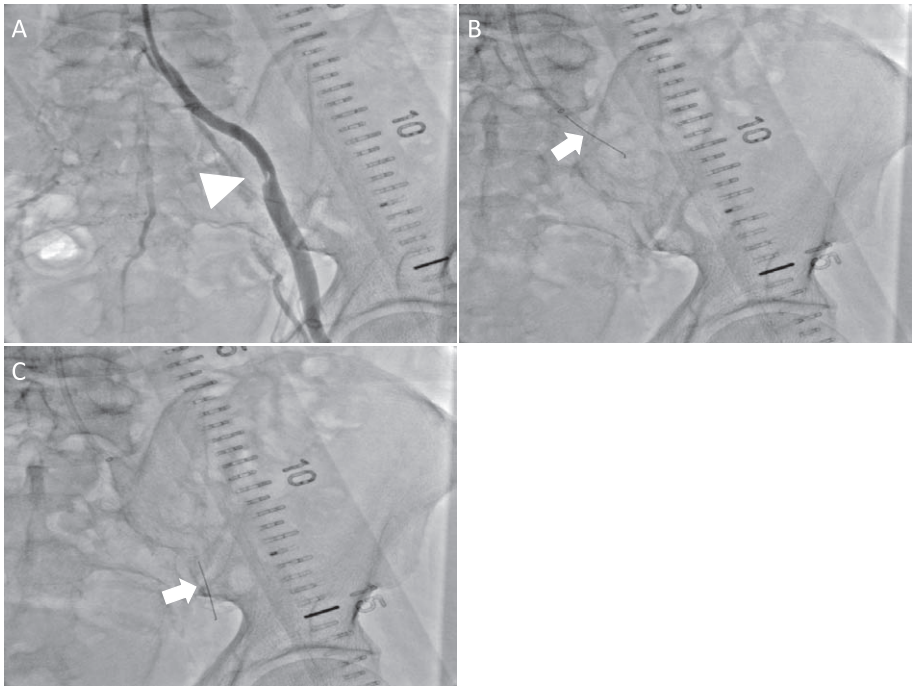

Fig. 1. pFFR measurement of a mildly stenotic lesion in the left external iliac artery
A : The delta shows mild stenosis of the left external iliac artery.
B : The pressure guidewire at the distal tip of the guide sheath measures the mean aortic pressure (arrow).
C : The pressure guidewire at the distal tip of the stenosis lesion measures the mean distal pressure (arrow).
pFFR, fractional flow reserve in peripheral artery disease.

guiding sheath (Destination®, Terumo, Tokyo, Japan) introduced via the contralateral approach.

All patients received intravenous heparin (5000 U) administration prior to placement of the guidewire. After confirming 50–75% stenosis of either the iliac artery or SFA by peripheral angiography, the tip of the guiding sheath was confirmed to be at a position where the peripheral blood flow was left undisturbed. A 0.014" pressure guidewire (St. Jude Medical, St. Paul, MN, USA) was advanced to the distal tip of the guiding sheath, the pressure was equalized, and then the mean aortic pressure (Pa) was measured after a 5 to 10-ml saline flush to remove contrast agent in the catheter. The guidewire was then advanced across the lesion for measuring the mean distal pressure (Pd) at baseline Pd / Pa (Fig. 1).

The optimal dose of papaverine hydrochloride for inducing maximum hyperemia was assessed in a preliminary investigation, as different doses of the agent were used in previous studies[9, 10, 16]. Hyperemia was induced with 10 mg of papaverine hydrochloride, the Pa and Pd measurements were repeated, and then pFFR was calculated as the ratio of mean Pd to mean Pa during hyperemia. While the pFFR thus calculated increased to 20 mg and 30 mg with a washout interval of 5 to 10 minutes between subsequent administrations, no significant difference in pFFR was found at different doses (Fig. 2). Therefore, the optimal papaverine hydrochloride dose for inducing hyperemia in this study was defined as 10 mg.

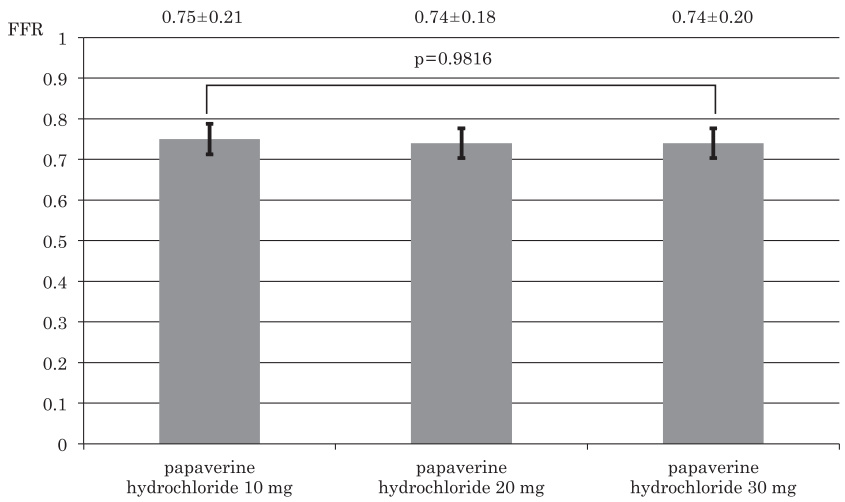

Fig. 2. pFFR following each papaverine hydrochloride dose (8 lesions). pFFR, fractional flow reserve in peripheral artery disease.

Three vasodilators were compared in the present study : ATP[7, 10], papaverine hydrochloride[8–10, 14], and isosorbide dinitrate. First, 100 μg of ATP was administered from the guiding sheath to determine the pFFR with a washout interval of 5 to 10 minutes. After confirming complete recovery to the baseline pFFR, 200 μg of ATP was administered. The same procedures were repeated after administration of 10 mg of papaverine hydrochloride and 1.5 mg of isosorbide dinitrate.

Statistical analysis

Continuous variables are expressed as means ± standard deviations and categorical variables are reported as percentages. Variable comparisons between groups were conducted using ANOVA & post hoc tests for continuous variables and Fisher's exact test for categorical variables. All analyses were performed using JMP software version 12 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

Table 1 details the characteristics of patients enrolled in this study. The patients had a mean age of 77 ± 1 (range 60–95) years and 18 patients were male (75.0%). Twenty patients (81.0%) had intermittent claudication and four (19.0%) had critical limb ischemia. Table 2 shows the types of lesions and procedures used. Of the 26 lesions, 14 (53.8%) were located in the SFA and 12 (46.2%) were located in the iliac artery ; 7 (26.9%) lesions underwent balloon angioplasty, 17 (65.4%) underwent stent placement, and 2 (7.7%) were deferred for EVT based on the pFFR results.

Effects of each vasodilator

Figure 3 shows the baseline Pd / Pa and pFFR results for the vasodilators examined. The

Table 1. Patient characteristics (26 lesions and 24 patients)

Variable	
Age, years	77 ± 1
Sex, male (%)	18 (75.0)
BMI, kg / m^2	21.2 ± 5.0
Hypertension (%)	20 (83.3)
Diabetes mellitus (%)	8 (33.3)
Insulin use (%)	2 (8.3)
Dyslipidemia (%)	16 (66.7)
Current smoker (%)	5 (20.8)
Past smoker (%)	9 (37.5)
Coronary artery disease (%)	13 (54.2)
Cerebral vascular disease (%)	2 (8.3)
Hemodialysis (%)	4 (16.7)
Clinical presentation	
Intermittent claudication (%)	20 (81.0)
Critical limb ischemia (%)	4 (19.0)
Fontaine	
I (%)	0 (0)
II (%)	20 (81.0)
III (%)	0 (0)
IV (%)	4 (19.0)
Rutherfold	
1 (%)	0 (0)
2 (%)	9 (28.6)
3 (%)	11 (52.4)
4 (%)	0 (0.0)
5 (%)	4 (19.0)
6 (%)	0
Medications	
Aspirin (%)	15 (62.5)
Clopidogrel (%)	12 (50.0)
Cilostazol (%)	8 (32.3)
Sarpogrelate (%)	4 (16.7)
Statin (%)	10 (41.7)
ACE / ARB (%)	11 (45.8)
Ca blocker (%)	10 (41.7)
β-blocker (%)	4 (16.7)

ACE : Angiotensin converting enzyme inhibitor
ARB : Angiotensin II receptor blocker

Table 2. Characteristics of the lesions and procedures used (26 lesions)

Variable	
Lesion characteristics	
SFA (%)	14 (53.8)
Iliac (%)	12 (46.2)
TASC classification	
A (%)	14 (53.8)
B (%)	12 (46.2)
Restenosis (%)	2 (7.7)
Vessel calcification (%)	10 (41.7)
Interventional results	
POBA (%)	7 (26.9)
STENT (%)	17 (65.4)
Deferred (%)	2 (7.7)
Number of stents	1.1 ± 0.3
Total stent length (mm)	45.3 ± 14.9
Mean stent diameter (mm)	7.7 ± 1.0
Number of run-off vessels	
0 (%)	1 (3.8)
1 (%)	6 (23.1)
2 (%)	10 (38.5)
3 (%)	9 (34.6)

TASC : TransAtlantic InterSociety Consensus
SFA : Superficial femoral artery
POBA : Plain old balloon angiography

baseline Pd / Pa (0.88 ± 0.08) decreased significantly after the use of every vasodilator ($P < 0.0001$), but there was no significant difference in the level of decrease among the vasodilators ($P = 0.7569$).

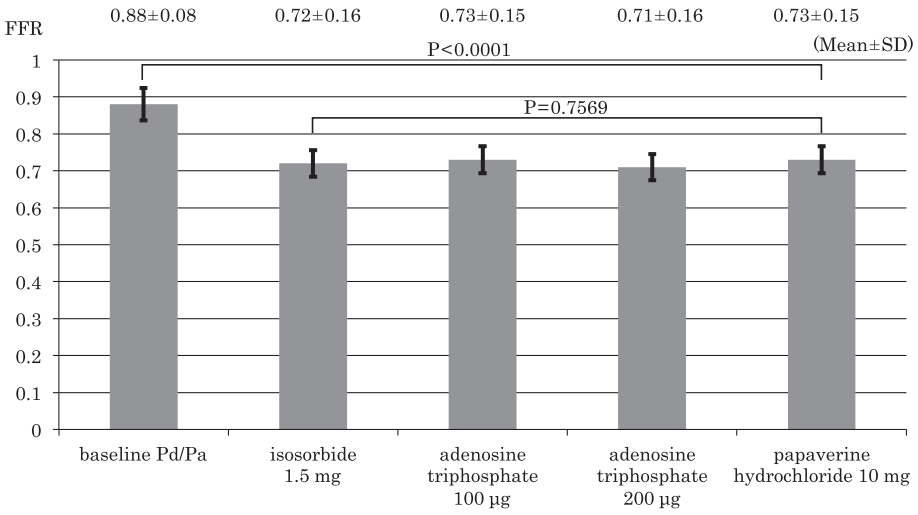

Fig. 3. Baseline Pd / Pa and pFFR obtained with each vasodilator (24 lesions)
Pd, mean distal pressure. Pa, mean aortic pressure. pFFR, fractional flow reserve in peripheral artery disease.

Vasodilator side effects

The study had to be discontinued in two patients with SFA lesions due to decreases in systemic blood pressure after vasodilator administration. In one case, the systolic blood pressure dropped to 60 mmHg after the administration of 10 mg papaverine hydrochloride, while in the other, the systolic blood pressure dropped to 58 mmHg after the administration of 1.5 mg isosorbide dinitrate.

Discussion

This is the first report comparing the effectiveness with which maximum hyperemia can be measured using various agents for the assessment of pFFR in PAD. The intra-arterial administration of ATP, papaverine chloride, and isosorbide dinitrate demonstrated similar effects in obtaining maximum hyperemia in pFFR, but the latter two agents induced systemic drops in blood pressure in two patients. Regarding the dose of ATP, a 100 μg dose of ATP was effective in achieving maximum hyperemia.

The maximum blood flow reserve of skeletal muscle is greater than that of the myocardium[11]; however, the muscle mass of the lower limbs varies much more between individuals compared to heart muscle, and the optimal vasodilator dose for obtaining maximum hyperemia depends on muscle mass[12, 13]. In addition, the degree to which a vasodilator expands a blood vessel might also differ from person to person. For these reasons, it is more difficult to determine the appropriate dose and type of vasodilator in pFFR than it is to measure FFR in PCI. Significant stenosis was traditionally defined physiologically as a mean arterial pressure difference greater than 10 mmHg[17], although passing a catheter through a lesion also induces a pressure gradient, even when using a small catheter such as a 4 Fr. Thus, a 0.014-inch pressure wire is superior to a small-size catheter in assessing the actual pressure gradient induced[6]. In the present study we

confirmed that the tip of the guiding sheath was placed at a position where the peripheral blood flow was left undisturbed on peripheral angiography. If the systolic pressure of the catheter became lower than that of the brachial pressure, we moved the catheter to a more proximal position, but not to a degree that would result in any difference between the sites. Papaverine has been reported to induce potential side effects such as hypotension, variable patient response[16, 18], and serious arrhythmia[19]. In addition, intra-coronary papaverine can prolong the QT interval, leading to polymorphic ventricular tachycardia and ventricular fibrillation. Although the mechanism underlying papaverine-induced QT prolongation is not fully understood, the drug can inhibit delayed rectifying potassium currents (IKr) and prolong the action potential duration. When the action potential duration is excessively prolonged, premature after-depolarization could provoke triggered activity and subsequent ventricular fibrillation[19]. Approximately half of all PAD patients are complicated with ischemic heart disease, so precautions to protect patients from serious arrhythmias are imperative. Thus, this study had to be discontinued in two patients with SFA lesions because of decreases in systemic blood pressure after receiving 10 mg of papaverine chloride or 1.5 mg of isosorbide dinitrate. Two of four patients taking beta-blockers in this study were also discontinued due to a decrease in systemic blood pressure. The administration of adenosine triphosphate 100 μg and 200 μg elicited no such decrease. The very short half-life (1 to a few seconds) of ATP makes it a useful agent for repeated evaluations of ischemia in multiple arteries without side effects[20].

In this preliminary study we determined that a 10 mg dose of papaverine hydrochloride was optimal for obtaining maximum hyperemia. The difference in the hyperemic dose of papaverine hydrochloride versus that was reported by Miki *et al*[16] may stem from differences in the target patients and vessels, as their study involved SFA lesions of normal subjects. Further, patients receiving papaverine hydrochloride have shown variable responses to the agent. Meanwhile, the 1.5 mg dose set for isosorbide dinitrate was based on empirically administered amounts in Japan. Finally, we set the ATP dose at 100 μg and 200 μg in the present study, based on a dose of 1 μg / kg in an earlier study and 200 μg in another study[7, 10].

Conclusions

The hyperemic efficacy of the intra-arterial administration of 100 μg of ATP was similar to the efficacies of 200 μg of ATP, 10 mg of papaverine hydrochloride, and 1.5 mg of isosorbide dinitrate. Given the milder side effects of ATP versus other vasodilators, ATP at an intra-arterial dose of 100 μg may be optimal as a first-line agent for pFFR measurement.

Conflict of interest disclosure

None.

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